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A new Co(0) complex mediated synthesis of *C*-glycoside analogues

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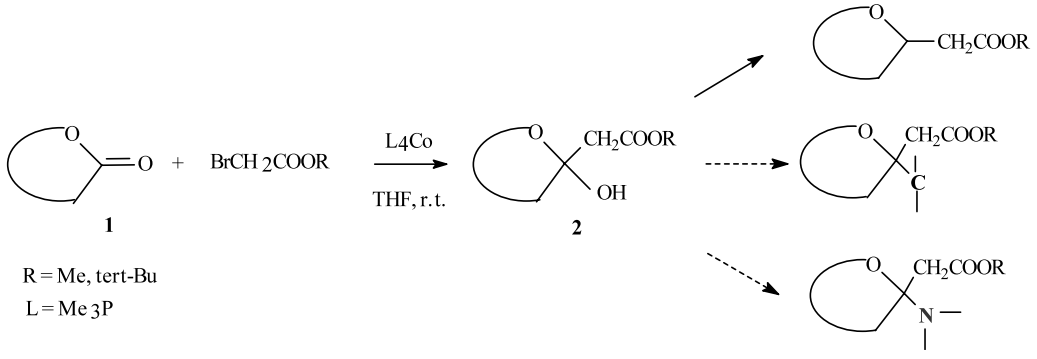
Abstract—Properly protected glyconolactones, readily available from the parent sugars, react under mild conditions with α-bromoacetates in the presence of a soluble Co(0) complex, either in stoichiometric or substoichiometric amounts, to give a Reformatsky-type addition product to the lactone. The addition product can be subsequently converted into a variety of compounds: dehydroxylation with triethylsilane in the presence of boron trifluoride affords *C*-glycosides.

1. Introduction

C-Glycosides are of considerable interest in carbohydrate chemistry, as well as in organic synthesis.[1] The stability of the *C*-glycosidic linkage (also present in several physiologically active natural products) to hydrolysis make *C*-glycosides particularly appealing for enzymatic and metabolic studies. In synthetic organic chemistry they are a readily accessible source of chiral synthons with more carbon functionalities than the corresponding *O*-glycosides, useful for the synthesis of complex natural products.

Several methods for carbon–carbon bond formation at the anomeric carbon have been reported in the literature:[2] the most common involves the attack of a carbon nucleophile (such as allyl silanes, silyl enol ethers, allylstannanes, homoenolates, Grignard reagents, organolithium, cuprates, aluminates, organozincs) on a variety of electrophilic sugars (such as glycosyl halides, thioglycosides, *O*-protected glycosides, imidates, lactones, glycals). Cycloadditions and sigmatropic rearrangements; free-radical approaches; transition-metal mediated reactions have also been reported.

Herein we report a mild and easy Co(0)- and/or Mg-mediated addition of α-bromoacetates to sugar lactones **1** to give lactols **2** (Scheme 1), potentially useful intermediates for the presence of the 'anomeric' hydroxyl which can be further elaborated to give a variety of compounds. For example they may be reduced with triethylsilane/boron trifluoride to give the correspond-



Scheme 1.

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ing *C*-glycosides, or used as scaffolds for the presentation of pharmacophores.

2. Results and discussion

The Co(0)-mediated addition of α-haloesters and α-haloketones to carbonyl compounds represents a mild and convenient procedure for the synthesis of β-hydroxy esters[3] and β-hydroxyketones.[4] A similar approach, applied to the reaction of α-halophosphonates and carbonyl compounds, yields β-hydroxyphosphonates, stable biomimetics of the corresponding phosphates.[5]

Table 1. Reactions of lactones **1a**–**1h** with *tert*-butyl-α-bromoacetate (R = benzyl group)

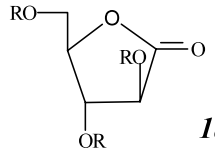
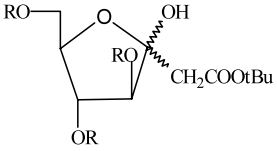
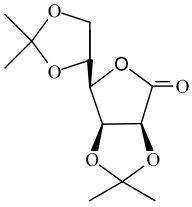
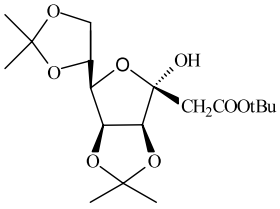
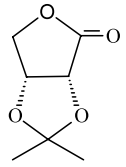
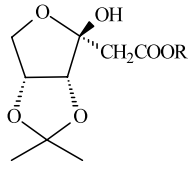
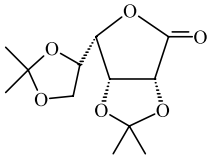
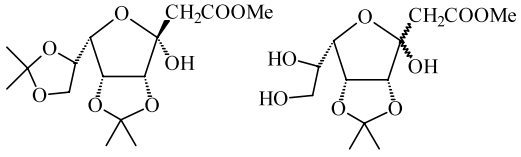
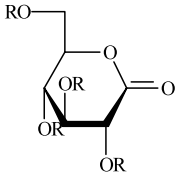
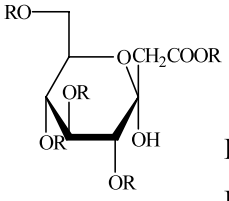
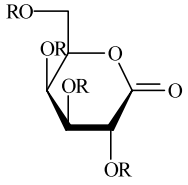
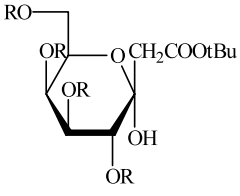
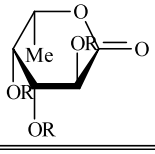
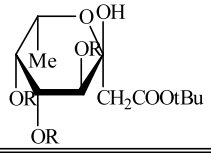
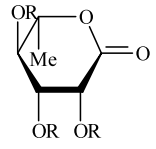
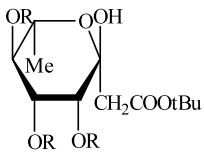
Lactone	Product	Yield (%)	Procedure[a]
 ***1a***	 ***2a***	73[25][c] d.r.=2/1 78[19][c] d.r.=2/1	A[d] B[d]
 **1b**	 **2b**	91 80	A[c] C[c]
 **1c**	 R= ^{t}Bu **2c** R= Me **2c'**	R = ^{t}Bu 55 [20][c] R = Me 50 [20][c]	B[d] B[d]
 **1d**	 **2d** **2d'**	**2d** 43 [6][c] **2d'** 41	B[d]
 **1e**	 R = tBu **2e** R = Me **2e′**	R = ^{t}Bu 90 88 R = Me 51 [8] 35 [12]	B C B C
 **1f**	 **2f**	91 95	B C
 **1g**	 **2g**	89	B

Table 1. (*Continued*)

 **1h**	 **2h**	55[25][c] 79	B C

a) **Procedure A**: lactone, tert-butyl α-bromoacetate and $[Co(PMe_3)_4]$ were used in a 1/1.2/1.2 ratio. **Procedure B**: a substoichiometric amount of $[Co(PMe_3)_4]$ (10%) was used in the presence of magnesium turnings. **Procedure C**: only magnesium turnings were used. b) 0.2-0.3 Molar solutions of lactone were used. c) The yields in brackets refer to recovered starting lactone.

Herein the Co(0)-mediated addition of α-haloesters and ketones to the carbon–oxygen double bond has been extended to sugar lactones. The final aim was the synthesis of compounds such as *C*-glycosides and analogues with potential biological activity.

For this purpose *tert*-butyl-α-bromoacetate was selected as a model compound for α-haloesters and reacted with a variety of sugar lactones, readily prepared from the corresponding sugars, in the presence of the Co(0) complex $(Me_3P)_4Co(0)$.[6,7] The results are summarized in Table 1.

As observed for the addition of haloesters to carbonyl compounds, the best results were obtained via a 'one-pot' procedure in which the two organic reagents were added simultaneously to the Co(0) complex using a 1.2/1.2/1 haloester/Co(0)/lactone mole ratio and 0.2–0.3 molar solution with respect to the lactone.

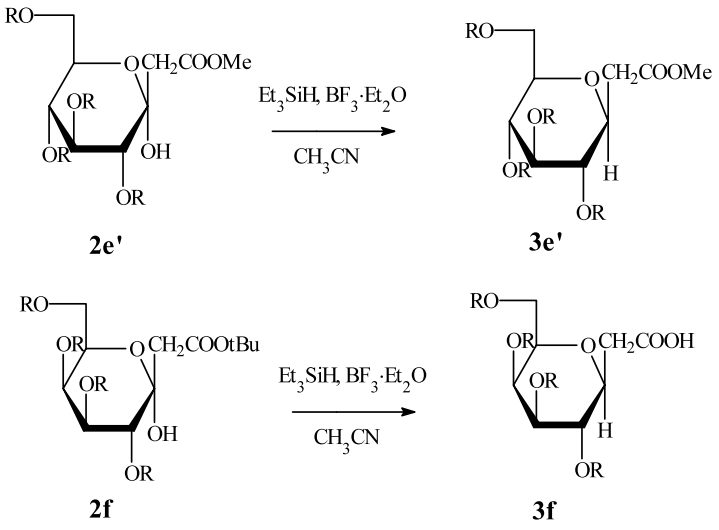
The reaction proceeded with good yields (73–91%). One stereoisomer was generally isolated with the exception of the lactone from 1,2,5-tri-*O*-benzyl-D-arabinofuranose which yielded two diastereomers in a 2:1 molar ratio. In some cases the starting lactone was found (10–25%), but was easily separated and recycled.

In the pyranose series (derivatives **2e**,[8,9] **2e′**,[8,9] **2f**,[8,9] **2g**[10] and **2h**), the configuration of the anomeric carbon has been assigned on the basis of literature data (where available) and NOEs which, in most cases, showed a correlation between one of the methylenic hydrogens of the CH_2COOR group and the hydrogen on the second carbon of the sugar moiety. The absence of NOEs between either methylenic hydrogens and the hydrogen on the fifth carbon of the sugar moiety further corroborated the equatorial orientation of the CH_2COOR residue. In the furanose series (derivatives **2b**,[11] **2c**,[12] **2c′**, **2d**[13]), the anomeric carbon configuration is suggested on the basis of literature data and through the multiplicity of the adjacent methylenic hydrogens, which has been used as a criterion: ulose sugars having a CH_2X group generally exhibit, in the NMR spectrum, a singlet for the CH_2 group when it is on the side of the furanose ring opposite to the ring hydroxyl groups. Otherwise, the signal appears as two doublets or a multiplet.[9,13] Albeit this empirical criterion has been in some cases validated by semi-empirical MO calculations, its general applicability could be questioned as no independent and direct configurational assignment for the anomeric centre was made.

We also found that the addition product was formed very cleanly when the reaction was carried out with a 10:1 mole ratio of the organic reagents to cobalt, provided that a sufficient quantity of magnesium metal was present to perform the reduction Co(II) to Co(0). The fact that the reaction can be carried out with a catalytic amount of the Co–phosphine complex offsets the disadvantage inherent to the use of trimethylphosphine, and make easier the purification of the product: in some cases the crude reaction product is pure enough to be directly used for further transformation without chromatographic purification. A further advantage is the color of the solution which continuously changes from yellow–brown [Co(0) complex] to dark blue–violet [Co(II) complex] during the addition of the organic reagents to the Co complex and allows an easy monitoring of the course of the reaction.

The addition of organometallic reagents to sugar lactones generally involves Grignard reagents, that allow the introduction of alkyl or phenyl groups, or organolithium compounds, which usually require strictly anhydrous conditions and low temperatures. A classical zinc-mediated Reformatsky reaction has been reported between the lactone of 2,3,5,6-di-*O*-isopropylidene-α-D-gulonofuranose and ethyl α-bromoacetate in dry dioxane at 50°C to afford the product corresponding to **2d** in 50% yield.[13] The same reaction performed using the Co(0) complex in substoichiometric conditions at room temperature afforded **2d** in 43% yields accompanied by 31% of a product derived from deprotection of position 5 and 6 of the sugar moiety, whose stereochemistry at the anomeric carbon remains however uncertain. Therefore, the Co(0)-mediated addition offers important advantages compared to the Zn-mediated Reformatsky reaction. First, the reaction is carried out under milder conditions. Second, the yield of the addition product may be higher. Third, the use of a soluble metallic complex offsets the problem of metal activation.

In order to test whether magnesium alone can be used and to what extent, the reactions of lactones **1a**–**h** with *tert*-butyl α-bromoacetate were also performed in the presence of activated magnesium turnings in tetrahydrofuran. The amount of bromoester, lactone and magnesium were the same used for the Co(0)-mediated



Scheme 2.

reactions under substoichiometric conditions. The addition product was generally obtained with reasonable to good yields (comparable at the best with those obtained in the Co-mediated reactions) albeit less reproducible and strongly dependent on the experimental conditions such as speed of stirring, time of reaction and, most of all, magnesium activation.

The addition products, the lactols **2** can be further elaborated to give a variety of biologically interesting compounds. For example they can be de-hydroxylated with triethylsilane to give the corresponding *C*-glycosides as reported in Scheme 2. This reaction has been verified on the glucose and galactose derivatives **2e**′ and **2f** which gave the corresponding *C*-glycosides **3e**′[14] and **3f** in 74 and 61% yields, respectively. In **3f** the *tert*-butyl ester was hydrolyzed under the acidic reaction conditions.

We previously obtained **3e**′ as a 2.5/1 diastereomeric mixture, albeit with very poor yields (10% from 1-chloro-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose), via a classical Reformatsky reaction between *tert*-butyl α-bromozinc acetate and 1-chloro-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (prepared from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose and thionyl chloride in dimethylformamide) in methylene chloride and in the presence of a silver compound (carbonate or triflate).[15] The corresponding 1-bromo-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (prepared from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose and hydrobromic acid in acetic acid) gave the same results.

Furthermore, derivatives **2e**, **2e**′ and **2f**′ have been already used as synthetic precursors for sugar-fused γ-aminobutyric acid analogs, where the GABA-pharmacophore has been engineered into the carbohydrate platform.[8]

3. Conclusions

With respect to known protocols, the reported procedure using a substoichiometric amount of Co(0) complex, represents a convenient alternative for the synthesis of the title compounds, with some advantages: mild experimental conditions; no requirement of strictly anhydrous and freshly distilled solvents; easy monitoring of the course and of the end point of the reaction; high stereoselection. When magnesium alone is used, the purification of the product is easier, but the reaction has the disadvantage of the heterogeneous conditions and it is less reproducible.

4. Experimental

Reagent grade tetrahydrofuran was refluxed over $LiAlH_4$ and distilled for magnesium-mediated reactions. For cobalt-mediated reactions dry tetrahydrofuran from Fluka was generally used, without further purification; occasionally absolute tetrahydrofuran from Fluka was used.

Reagent grade dichloromethane was refluxed over P_2O_5 and distilled. 2,3,5-Tri-*O*-benzyl-β-D-arabinofuranose, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose and 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose were purchased from Sigma and converted to the corresponding lactones **1a**,[16] **1b**[17] and **1e**[18] according to the procedure reported below. 2,3,4-Tri-*O*-benzyl-L-fucopyranose, 2,3,4,6-tetra-*O*-benzyl-galactopyranose and 2,3,4-tri-*O*-benzyl-L-rhamnopyranose were purchased from Toronto Research Chemicals (Canada) and converted to the corresponding lactones **1g**,[19] **1f**[20] and **1h**[21] according to the procedure reported below. 2,3-*O*-Isopropylidene-D-erythronolactone and 2,3:5,6-di-*O*-isopropylidene-α-D-gulonofuranose were purchased from Aldrich. Proton and carbon nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded at 200 and 300 MHz on Brucker spectrometers. MS spectra were recorded with a VG7070 E9 spectrometer. Melting points were obtained by using a Buchi 535 apparatus. The $[\alpha]_D$ were obtained with a Perkin–Elmer 241 Polarimeter and the elemental analyses for the new compounds were determined on a Perkin–Elmer 240 Analyser. Flash-column

chromatographs were performed on silica gel Merck Kieselgel 60 (230–400 mesh ASTM). Thin-layer chromatographs were performed on silica gel plates (60 F254, Merck): spots were detected visually by ultraviolet irradiation (254 nm) or by spraying with methanol:H_2SO_4 9:1, followed by heating at 100°C. All reactions were performed in a dry nitrogen atmosphere, using glassware dried by flaming in a stream of dry nitrogen.

Typical procedure for the synthesis of glyconolactones. A solution of a properly protected sugar (1 mmol) in dry methylene chloride (5 mL) was added under nitrogen to a suspension of pyridiunium chlorochromate (0.75 g, 3.5 mmol) and molecular sieves (0.3 mm from Merck, 0.5 g) in methylene chloride (2 mL). The reaction mixture was stirred under nitrogen in the dark and was monitored by thin-layer chromatography (silica gel, eluting with ethylacetate:petroleum ether 6:4). At the end of the reaction, the reaction mixture was filtered over silica gel eluting with ethylacetate:petroleum ether 4:6. Removal of the solvent under reduced pressure afforded the glyconolactone (80–85% yields) which was directly used.

Typical procedure for the stoichiometric reaction mediated by $(Me_3P)_4Co$ (Procedure A). A 1 M solution of trimethylphosphine in tetrahydrofuran (6 mL) was added to a mixture of activated magnesium turnings[22] (ca. 0.3 g) and anhydrous $CoCl_2$ (0.19 g, 1.5 mmol). The reaction mixture was stirred at room temperature till a dark brown color developed.[23] The excess of magnesium was filtered off, and to the resulting solution were added *tert*-butyl α-bromoacetate (1 mmol, 0.15 mL) and the lactone (1 mmol) in tetrahydrofuran, dropwise over a period of 1 h. The reaction was monitored by thin-layer chromatography (silica gel, eluting with ethylacetate–petrolum ether 7/3).

Two different work up procedures were used depending on the water-solubility of the lactone and of the product. For water-unsoluble compounds the reaction mixture was stirred in the air until a blue color developed, diluted with ethyl acetate and poured into crushed ice/aqueous HCl. The aqueous phase was extracted with ethylacetate (3×15 mL). The organic layers were collected, dried (Na_2SO_4), and evaporated to dryness. Occasionally a light blue or green color still persistent in the crude material was eliminated by dissolving in ethyl acetate and by washing with a saturated EDTA (bis-sodium salt) solution.

The crude material was chromatographed on silica gel, eluting with ethylacetate:petroleum ether 7:3 and ethyl acetate:methanol 9:1, to separate the product from unreacted starting lactone.

For partially soluble compounds, the reaction mixture was filtered on silica gel eluting with ethyl acetate:petroleum ether to remove cobalt salts. The crude material was then chromatographed on silica gel as described above. Trimethylphosphine can be conveniently substituted with triphenylphosphine without affecting the course of the reaction.

Typical procedure for the substoichiometric reaction mediated by $(Me_3P)_4Co$ (Procedure B). A 1 M solution of trimethylphosphine in dry tetrahydrofuran (1 mL) was added to a mixture of activated magnesium turnings (0.3 g)[24] and anhydrous $CoCl_2$ (0.032 g, 0.25 mmol) in tetrahydrofuran (2 mL). The mixture was stirred at room temperature till the brown color of the cobalt(0) complex developed. A tetrahydrofuran solution (10 mL) of lactone (1 mmol) and *tert*-butyl-α-bromoacetate (1.2 mmol, 0.18 mL) was added dropwise under stirring. The speed of addition was modulated so as to reduce to a minimum the time of persistence of the blue color (Co(II) complex) developed during the addition. The reaction was monitored by thin-layer chromatography (silica gel, eluting with ethyl acetate:petroleum ether 7:3). Trimethylphosphine can be conveniently substituted with triphenyl phosphine without affecting the course of the reaction.

At the end of the reaction, also indicated by the persistence of the brown color of the original Co(0) complex, the magnesium was filtered off and the resulting solution was stirred in the air till a blue color developed. For water-unsoluble compounds it was then diluted with ethyl acetate and washed with diluted HCl as described above. The aqueous phase was extracted with ethylacetate (3×15 mL). The organic layers were collected, dried (Na_2SO_4), and evaporated to dryness. Occasionally a light blue or green color still persistent in the crude material was eliminated by dissolving in ethyl acetate and by washing with a saturated EDTA (bis-sodium salt) solution.

For water-soluble compounds occasionally few drops of methanol were added to the blue tetrahydrofuran solution to destroy traces of magnesium metal still present and the solvent was therefore removed under reduced pressure. The residue was taken up in ethyl acetate and filtered on silica gel eluting with ethyl acetate–petroleum ether. The crude material was then chromatographed as described above.

2a. Colorless syrup. ^{1}H NMR ($CDCl_3$): δ (minor), 1.45 (s, 9H), 2.6 and 2.73 (2H, AB system, $J=15.0$ Hz); ^{13}C NMR ($CDCl_3$): (minor), 28.08 (q), 42.98 (t), 71.61 (t), 72.73 (t), 80.38 (d), 84.21 (d), 85.61 (d).

^{1}H NMR ($CDCl_3$); δ (major), 1.45 (s, 9H), 2.77 (s, 2H), 3.52 and 3.58 (2H, ABX system, $J=10.3$, 5.9, 5.9 Hz), 3.94 (dd, 1H, $J=4.4$, 3.6 Hz), 4.07 (d, 1H, $J=3.6$ Hz), 4.33 (dd, 1H, $J=5.9$, 5.9 Hz), 4.47 (s, 2H), 4.52 (s, 2H), 4.57 (s, 2H), 5.0 (s, 1H, disappears with D_2O). ^{13}C NMR ($CDCl_3$): δ (major), 3×28.08 (q), 40.38 (t), 70.07 (t), 71.90 (s), 71.93 (t), 73.38 (t), 82.22 (d), 81.65 (s), 82.69 (d), 87.70 (d), 104.79 (s), 6×127.77 (d), 3×128.08 (d), 6×128.38 (d), 137.68 (s), 137.8 (s), 137.94 (s), 171.22 (s); MS, m/z: 327 (M^+–CH_2Ph–CH_3COO^tBu), 107 ($PhCH_2O$), 91 ($PhCH_2$). Anal. calcd for $C_{32}H_{38}O_7$: C, 71.91%; H, 7.12%. Found: C, 71.74%; H, 7.33%.

2b.[11] Colorless crystals; mp 102–103°C (petroleum ether–ethyl acetate); $[\alpha]_D^{25}$ +12.4 ($CHCl_3$, c 10 mg/mL); ^{1}H NMR ($CDCl_3$): δ 1.3 (s, 3H), 1.35 (s, 3H), 1.4 (s,

3H), 1.43 (s, 3H), 1.44 (s, 9H), 2.62 and 2.69 (AB system, 2H, $J=16.5$ Hz), 3.96 (dd, 1H, $J=7.8$, 5.5 Hz), 4.03 (dd, 1H, $J=7.8$, 5.8 Hz), 4.07 (dd, 1H, $J=7.5$, 5.5 Hz), 4.13 (ddd, 1H, $J=7.5$, 5.8, 5.5 Hz), 4.45 (d, 1H, $J=6.0$ Hz), 4.82 (dd, 1H, $J=6.0$, 4.5 Hz); ^{13}C NMR ($CDCl_3$): 24.39 (q), 25.02 (q), 25.32 (q), 26.75 (q), 3×27.97 (q), 39.23 (t), 66.78 (t), 73.02 (d), 79.25 (d), 80.13 (d), 82.02 (s), 85.72 (d), 103.97 (s), 109.05 (s), 112.7 (s), 171.36 (s); MS m/z: 359 (M^+-CH_3), 302 ($M^+-CH_3-O'Bu$), 259 ($M^+-CH_2COO'Bu$), 115 ($CH_2COO'Bu$). Anal. calcd for $C_{18}H_{30}O_8$: C, 57.75%; H, 8.02%. Found: C, 56.82%; H, 8.04%.

2c.[12] Colorless syrup; $[\alpha]_D^{25}=-48.5$ ($CHC1_3$, c 10.50 mg/mL); ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 3H), 1.46 (s, 3H), 1.48 (s, 9H), 2.72 and 2.78 (AB system, $J=16.5$ Hz), 3.94 (d, 1H, $J=10.5$ Hz), 4.07 (1H, dd, $J=10.5$, 3.4 Hz), 4.43 (d, 1H, 6. 0 Hz), 4.85 (dd, 1H, $J=6.0$, 3.4 Hz); ^{13}C NMR ($CDCl_3$): 24.80 (q), 26.23 (q), 3×28.07 (q), 39.15 (t), 72.23 (t), 80.55 (d), 82.21 (s), 85.38 (d), 104.55 (s), 112.49 (s), 171.82 (s); MS, m/z: 259 (M^+-CH_3), 201 ($M^+-OC(CH_3)$), 159 ($M^+-CH_2COO'Bu$), 143 ($201-CH_3COOCH_3$). Anal. calcd for $C_{13}H_{22}O_6$: C, 56.93%; H, 8.03%. Found: C, 56.74%; H, 8.05%.

2c′. Colorless syrup; $[\alpha]_D^{25}$ −45.7 ($CHC1_3$, c 10.46 mg/mL); ^{1}H NMR ($CDCl_3$): δ 1.25 (s, 3H), 1.40 (s, 3H), 2.75 and 2.88 (2H, AB system, $J=17.5$ Hz), 3.72 (s, 3H), 3.90 (d, 1H, $J=10.0$ Hz), 4.0 (dd, 1H, $J=10.0$, 4.0 Hz), 4.43 (d, 1H, $J=5.5$ Hz), 4.82 (dd, 1H, $J=5.5$, 4. 0 Hz); ^{13}C NMR ($CDCl_3$): 24.78 (q), 26.16 (q), 38.29 (t), 51.87 (q), 71.22 (t), 80.52 (d), 85.13 (d), 104.38 (s), 112.54 (s), 172.49 (s); MS, m/z: 232 (M^+), 217 (M^+-CH_3), 201 (M^+-OCH_3), 159 ($M^+-CH_2COOCH_3$), 73 (CH_2COOCH_3). Anal. calcd for $C_{10}H_{16}O_6$: C, 51.72%; H, 6.90%. Found: C, 51.74%; H, 6.53%.

2d. Colorless syrup $[\alpha]_D^{25}$ −11.6 ($CHCl_3$, c 4.2 mg/mL); ^{1}H NMR ($CDCl_3$): δ 1.25 (s, 3H), 1.38 (s, 3H), 1.52 (s, 6H), 2.86 and 2.87 (AA′ system, $J=18$ Hz), 3.72 (s, 3H), 3.65–3.72 (m, 2H), 4.08 (dd, 1H, $J=7.5$, 4.5 Hz), 4.18 (t, 1H, $J=7.5$ Hz), 4.3 (ddd, 1H, $J=7.5$, 7.5, 7.5 Hz), 4.52 (d, 1H, $J=6.0$ Hz), 4.70 (dd, 1H, $J=6.0$, 4.5 Hz); ^{13}C NMR ($CDCl_3$): 24.39 (q), 25.88 (q), 38.24 (t), 51.98 (q), 63.54 (t), 70.70 (d), 78.98 (d), 80.70 (d), 86.06 (d), 103.50 (s), 113.0 (s), 172.44 (s); MS, m/z: 332 (M^+), 317 (M^+-CH_3), 301 (M^+-OCH_3), 259 ($M^+-CH_2COOCH_3$), 73 (CH_2COOCH_3). Anal. calcd for $C_{15}H_{24}O_8$: C, 54.22%; H, 7.23%. Found: C, 54.52%; H, 7.53%.

2d′. Colorless syrup; $[\alpha]_D^{25}$ −14.8 ($CHC1_3$, c 3.5 mg/mL); ^{1}H NMR ($CDCl_3$): δ 1.31 (s, 3H), 1.48 (s, 3H), 2.83 and 2.92 (AB system, 2H, $J=16.6$ Hz), 3.74 (s, 3H), 3.65–3.80 (m, 2H), 4.05 (ddd, 1H, $J=4.0$, 4.0, 4. 0 Hz), 4.16 (dd, 1H, $J=6.0$, 4. 0 Hz), 4.53 (d, 1H, $J=6.$ 0 Hz), 4.81 (dd, 1H, $J=6.0$,4.0 Hz); ^{13}C NMR ($CDCl_3$): 24.68 (q), 25.42 (q), 25.94 (q), 38.07 (t), 51.93 (q), 66.05 (t), 75.56 (d), 80.34 (d), 81.88 (d), 85.55 (d), 85.89 (d), 104.03 (s), 109.75 (s), 112.86 (s); MS, m/z: 292 (M^+), 231 ($M^+-CH(OH)CH_2(OH)$), 213 ($231-H_2O$),107 ($PhCH_2O$),98 ($213-C(CH_3)_2-CH_2COOCH_3$), 73 ($CH_2COOCH_3$). Anal. calcd for $C_{12}H_{20}O_8$: C, 49.32%; H, 7.85%. Found: C, 49.74%; H, 7.83%.

2e.[8] Colorless syrup. $[\alpha]_D^{25}$: 3.6 ($CHCl_3$, c 17.9 mg/mL); ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H), 2.28 (d, 1H, $J=15.0$ Hz), 2.73 (d, 1H, $J=15.0$ Hz), 3.3 (d, 1H, $J=9.0$ Hz), 3.60 (dd, 1H, $J=10.5$, 1.5 Hz), 3.68 (dd, 1H, $J=9.0$, 9.0 Hz), 3.73 (dd, 1H, $J=10.5$, 3.0 Hz), 4.30 (ddd, 1H, $J=9.0$, 3.0, 1.5 Hz), 4.12 (dd, $J=9.0$, 9.0 Hz), 4.5–4.7 (4 H), 4.85 (d, 1H, $J=12.0$ Hz), 4.90 (s, 2H), 4.95 (d, 1H, $J=12.0$ Hz); ^{13}C NMR ($CDCl_3$): 3×28.07 (q), 41.59 (t), 68.81 (t), 71.39 (d), 73.42 (t), 74.85 (t), 75.30 (t), 75.61 (t), 77.46 (d), 78.62 (d), 82.27 (d), 83.18 (d), 97.22 (s), 8×127.60 (d), 4×127.79 (d), 8×128.37 (d), 1347.95 (s), 138.38 (s), 138.40 (s), 138.64 (s), 171.68 (s); MS, m/z: 536 ($M^+-H_2O-COO'Bu$), 429 ($536-PhCH_2O$), 337 ($429-PhCH_2OH$), 107 ($PhCH_2O$), 91 ($PhCH_2$). Anal. calcd for $C_{40}H_{46}O_8$: C, 73.39%; H, 7.03%. Found: C, 73.48%; H, 7.33%.

2e′.[8] Colorless syrup. $[\alpha]_D^{25}$ −10.1 ($CHCl_3$, c 17.8 mg/mL); ^{1}H NMR ($CDCl_3$): δ 2.34 (d, 1H, $J=16.0$ Hz), 2.75 (d, 1H, $J=16.0$ Hz), 3.34 (d, 1H, $J=8.0$ Hz), 3.61 (dd, 1H, $J=10.5$, 2.0 Hz), 3.66 (s, 3H), 3.69 (dd, 1H, $J=9.5$, 8.0 Hz), 3.73 (dd, 1H, $J=10.5$, 4.0 Hz), 4.01 (ddd, $J=9.5$, 4.0, 2.0 Hz), 4.13 (dd, 1H, $J=8.0$, 8.0 Hz), 4.49 and 4.56 (AB system, $J=12.0$ Hz), 4.59 (d, 1H, $J=12.0$ Hz), 4.65 (d, 1H, $J=12.0$ Hz), 4.84 (d, 1H, $J=12.0$ Hz), 4.91 (s, 2H), 4.96 (d, 1H, $J=12.0$ Hz); ^{13}C NMR ($CDCl_3$): 40.32 (t), 51.69 (t), 68.59 (t), 71.46 (d), 73.19 (t), 74.81 (t), 75.46 (t), 75.56 (t), 78.46 (d), 81.76 (d), 83.11 (d), 96.02 (s), 8×122.71 (d), 4×124.40 (d), 8×128.31 (d), 137.79 (s), 2×138.24 (s), 138.52 (s), 172.71 (s); MS, m/z: 594 (M^+-H_2O), 521 (M^+-CH_2COOMe), 503 ($521-H_2O$), 91 ($PhCH_2$). Anal. calcd for $C_{37}H_{40}O_8$: C, 72.55%; H, 6.54%. Found: C, 72.48%; H, 6.53%.

2f.[8] Colorless syrup. ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 9H). 2.35 (d, 1H, $J=15.5$ Hz), 2.78 (d, 1H, $J=15.5$ Hz), 3.48 (dd, 1H, $J=9.0$, 6.0 Hz), 3.59 (dd, 1H, $J=9.0$, 7.5 Hz), 3.77 (d, 1H, $J=9.3$ Hz), 4.02 (dd, 1H, $J=2.5$, 1.5 Hz), 4.09 (dd, 1H, $J=9.3$, 2.5 Hz), 4.17 (ddd, 1H, $J=7.5$, 6.0, 1.5 Hz), 4.40 and 4.48 (AB System, 2H, $J=12.0$ Hz), 4.61 (s, 2H), 4.63 (d, 1H, $J=12.0$ Hz), 4.95 (d, 1H, $J=12.0$ Hz), 4.98 (d, 1H, $J=12$ Hz). ^{13}C NMR ($CDCl_3$): 3×28.02 (q), 41.59 (t), 68.91 (t), 70.07 (d), 72.67 (t), 73.41 (t), 74.70 (t), 74.99 (d), 75.32 (t), 78.62 (d), 80.41 (d), 82.08 (s), 97.74 (s), 4×127.55 (d), 2×127.71 (d), 2×127.84 (d), 4×128.18 (d), 8×128.38 (d), 2×138.12 (s), 138.53 (s), 138.81 (s), 171.86 (s); MS, m/z: 636 (M^+-H_2O), 536 ($636-COO'Bu$), 337 ($429-PhCH_2OH$), 107 ($PhCH_2O$), 91 ($PhCH_2$). Anal. calcd for $C_{40}H_{46}O_8$: C, 73.39%; H, 7.03%. Found: C, 73.58%; H, 7.43%.

2g. Colorless syrup. $[\alpha]_D^{25}$ +4.5 ($CHC1_3$, c 10.5 mg/mL); ^{1}H NMR ($CDCl_3$) δ 1.1 (d, 3H, $J=7.1$ Hz), 1.42 (s, 9H), 2.32 (d, 1H, $J=15.0$ Hz), 2.76 (d, 1H, $J=15.0$ Hz), 3.68 (dd, 1H, $J=3.0$, 1.0 Hz), 3.78 (d, 1H, $J=10.5$ Hz), 4.18 (dd, 1H, $J=10.5$, 3.0 Hz), 4.19 (dq, 1H, $J=7.2$, 1.0 Hz), 4.69 (d, 1H, $J=12.0$ Hz), 4.70 (d, 1H, $J=12.0$ Hz), 4.76 (s, 2H), 4.97 (d, 1H, $J=12.0$ Hz), 4.99 (d, 1H, $J=12.0$ Hz), 7.25–7.4 (15H); ^{13}C NMR ($CDCl_3$): 16.54 (q), 3×27.96 (q), 41.66 (t), 66.94 (d),

72.73 (t), 74.85 (t), 75.22 (t), 77.51 (d), 77.64 (d), 78.45 (d), 80.75 (d), 82.0 (s), 97.49(s), 3×127.52 (d), 6×128.13 (d), 6×128.36 (d), 139.17 (s), 139.53 (s), 139.61 (s), 172.01 (s); MS m/z: 530 (M^+-H_2O), 423 (530–$PhCH_2O$), 91 ($PhCH_2$). Anal. calcd for $C_{33}H_{40}O_7$: C, 72.26%; H, 7.30%. Found: C, 72.74%; H, 7.53%.

2h. Colorless syrup. $[\alpha]_D^{25}$ −5.7 ($CHC1_3$, c 12.75 mg/mL); ^1H NMR ($CDCl_3$): δ 1.25 (d, 3H, $J=6.2$ Hz), 1.48 (s, 9H), 2.22 (d, 1H, $J=15.0$ Hz), 2.85 (d, 1H, $J=15.0$ Hz), 3.62 (dd, 1H, $J=9.6$, 9.6), 3.74 (d, 1H, $J=3.0$ Hz), 3.91 (dq, 1H, $J=9.6$, 6.2 Hz), 4.12 (dd, 1H, $J=9.6$, 3.0 Hz), 4.65 (d, 1H, $J=12.0$ Hz), 4.68 (d, 1H, $J=12.0$ Hz), 4.92 (d, 1H, $J=12.0$ Hz), 4.98 (d, 1H, $J=12.0$ Hz), 4.7 (s, 2H), 7.257.4 (15 H); ^{13}C NMR ($CDCl_3$): 17.96 (q), 3×28.03 (q), 41.36 (t), 68.62 (d), 72.90 (t), 74.57 (t), 75.15 (t), 77.87 (d), 80.52 (d), 81.39 (d), 82.09 (s), 97.33 (s), 4×127.55 (d), 127.60 (d), 2×127.66 (d), 2×128.05 (d), 4×128.29 (d), 4×128.41 (d), 138.70 (s), 172.20 (s); MS m/z: 530 (M^+-H_2O),423 (530–$PhCH_2O$), 91 ($PhCH_2$). Anal. calcd for $C_{33}H_{40}O_7$: C, 72.26%; H, 7.30%. Found: C, 72.54%; H, 7.28%.

3e′.[22] Colorless crystals; mp = 66–67°C (petroleum ether–ethyl acetate); $[\alpha]_D^{25}$: 3.2 ($CHC1_3$, c 12.1 mg/mL); ^1H NMR ($CDCl_3$): δ 2.48 (dd, 1H, $J=16.7$, 8.5 Hz), 2.75 (dd, 1H, $J=16.7$, 3.9 Hz), 3.37 (dd, 1H, $J=9.5$, 9.5 Hz), 3.47 (ddd, 1H, $J=9.5$, 3.0, 3.0 Hz), 3.61 (s, 3H), 3.65 (dd, 1H, $J=9.5$, 9.5 Hz), 3.70 (d, 2H, $J=3.0$ Hz), 3.73 (dd, 1H, $J=9.5$, 9.5 Hz), 3.76 (ddd, 1H, $J=9.5$, 8.5, 3.9 Hz), 4.52 (d, 1H, $J=12.0$ Hz), 4.60 (d, 1H, $J=12.0$ Hz), 4.61 (d, 1H, $J=12.0$ Hz), 4.82 (d, 1H, $J=12.0$ Hz), 4.88 and 5.92 (AB system, 2H, $J=12.0$ Hz), 5.93 (d, 1H, $J=12.0$ Hz), 7.15-7.35 (20H); ^{13}C NMR ($CDCl_3$): 34.94 (t), 49.08 (q), 66.20 (t), 70.86 (t), 72.99 (t), 73.39 (d), 76.01 (d), 76.90 (d), 78.03 (d), 84.66 (d), 3×125.15(d), 6×125.30 (d), 6×125.9 (d), 135.55 (s), 2×135.76 (s), 136.01 (s), 168.87 (s); MS, m/z: 596 (M^+-1), 5 81 (M^+-CH_3), 505 (M^+-PhCH_2), 91 ($PhCH_2$). Anal. calcd for $C_{37}H_{40}O_7$: C, 74.5%; H, 6.7%. Found: C, 73.94%; H, 7.00%.

3f. Colorless oil; $[\alpha]_D^{25}$ +20.5 ($CHC1_3$, c 11. 3 mg/mL); ^1H NMR ($CDCl_3$): δ 2.72 and 2.74 (AA′X system, 2H, $J_{AX}=10.5$ Hz, $J_{A'X}=7.5$ Hz), 3.52 (dd, 1H, $J=9.0$, 6.0 Hz), 3.5–3.66 (m, 3H), 3.75 (ddd, 1H, $J=6.0$, 6.0, 1.5 Hz), 3.78 (dd, 1H, $J=9.0$, 3.5 Hz), 4. 0 (dd, 1H, $J=3.5$, 1.5 Hz), 4.45 (AB system 2H, $J=12.0$ Hz), 4.46 (d, 1H, $J=9.0$ Hz), 4.57 (d, 2H, $J=10.5$ Hz), 4.67 (d, 1H, $J=12.0$ Hz), 4.88 (d, 1H, $J=12.0$ Hz), 4.98 (d, 1H, $J=10.5$ Hz), 7.2–7.42 (m, 20H); ^{13}C NMR ($CDCl_3$): 34.96 (t), 68.67 (t), 72.15 (t), 73.58 (t), 75.62 (t), 76.27 (t), 75.87 (d), 76.82 (d), 80.16 (d), 80.52 (d), 81.51 (d), 127.43 (d), 3×127.65 (d), 4×127.76 (d), 4×128.19 (d), 8×128.34 (d), 2×137.65 (s), 138.12 (s), 138.21 (s), 172.08 (s); MS, m/z: 474 (M^+-PhCH_2OH), 414 (474–CH_3COOH), 91 ($PhCH_2$). Anal. calcd for $C_{36}H_{38}O_7$: C, 74.23%; H, 6.53%. Found: C, 74.54%; H, 6.71%.

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23. The solution can also be warmed with an external bath at ca. 50°C to speed the reduction of Co(II) to Co(0). Warming may be useful when triphenylphosphine is used instead of trimethylphosphine.
24. Magnesium metal is used in excess and can be recycled after use.